Merck Research Laboratories
HER2 and CEA Plasmid Vaccine

The scientfic abstract

Cancer vaccine trials have demonstrated that it is possible to elicit a tumor-antigen-specific immune response that ultimately may contribute to an antitumor effect. In this context, the use of plasmid DNA as vehicle for vaccination offers the possibility of targeting multiple antigens and to repeatedly vaccinate the patient without eliciting neutralizing immune responses to the vector. Nonetheless, plasmid DNA vaccination has suffered, to date, from the lack of significant efficacy in a variety of preclinical and clinical studies that are due, at least in part, to the limited transduction efficiency of muscle and antigen presenting cells (APC). The efforts carried out at Merck have been to evaluate in preclinical models the immunogenic potency of a vaccine based on plasmid DNA electroporation (DNA-EP). We have repeatedly demonstrated in a variety of animal models that DNA-EP increases the transfection efficiency of muscle cells leading to an enhanced gene expression and immunogenicity of the target antigen. Our hypothesis is that, as observed in preclinical models, DNA-EP will demonstrate greater efficacy of vaccination in view of the improved delivery of plasmid DNA. The vaccination trial will be based on the combined use of vectors encoding HER2 and carcinoembryonic antigen (CEA). The choice of immunizing with two antigens is based on the consideration that tumor development is the consequence of aberrant expression of multiple proteins and thus, targeting the immune response against multiple antigens that play a role in the process of tumor formation and spread may prove to be more effective than focusing on a single antigen. To further enhance their immunogenic properties, we have modified the DNA encoding CEA and HER2 by using codon-optimized sequences to improve the translation efficiency of the mRNA. This modification has been shown to enhance antigen expression in a variety of experimental models. Additionally, the HER2 construct used in this study encodes only the extracellular and transmembrane domains (ECDTM) for safety considerations. However, in preclinical studies we have demonstrated that HER2-ECDTM is more immunogenic than the full length protein. The CEA construct encodes the tumor antigen fused at its C-terminus to the B subunit of heat labile enterotoxin (CEA-LTB). This fusion protein was chosen as immunogen in view of our data obtained in preclinical studies demonstrating that it is significantly more immunogenic than the wild type CEA.

The aims of this trial are to: (a) determine the safety of a plasmid DNA vaccine administered in conjunction with EP to cancer patients whose tumors express CEA and/or HER2; (b) determine the immunogenicity of DNA-EP vaccine for CEA and HER2; and (c) assess whether the dose of the CEA and HER2 plasmids impacts the development of an immune response to these target antigens.